# Freezer Burn: Egg Banking Is a Growth Industry

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The viability of a woman's eggs declines in her mid 30s and drops precipitously in her 40s. A healthy older woman can still carry a pregnancy successfully if she uses eggs from a younger donor. What if she could freeze her own eggs? After all, IVF, or in vitro fertilization, so radical when introduced in the mid 80s, is now commonplace. According to Fertile Hope (http://www.fertilehope.org), an organization that promotes fertility research for cancer patients, 139 fertility clinics in the U.S. and two companies are now entering the frozen egg business.

Egg freezing could be a godsend for women who are facing cancer treatments or other medical procedures that could impair fertility, have family members experiencing early menopause, or object to discarding left over embryos after IVF because of personal or religious reasons. But a bigger market lurks: healthy women who delay childbearing or worry that they won't meet the right partner in time and are seeking a bit of insurance to safeguard their fertility.

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"Our studies show that egg freezing allows pregnancy rates comparable to fresh eggs," says Dr. Seang Lin Tan, director of the McGill Reproductive Centre. Tan's team has developed a procedure called IVM, or in vitro maturation, which involves extracting immature eggs without using fertility drugs, maturing them in a dish, and vitrifying them in a protective device called a Cryoleaf. So far, Tan's team has tried this procedure in two studies that included a total of 36 women under 35 and obtained a pregnancy rate of over 40 percent. Treatments cost U.S. $4000 a cycle and $2400 for cancer patients.

## Banking on Liquid Nitrogen Instead of Luck

While C. Chen published a paper in the *Lancet* in 1986 detailing a pregnancy from frozen eggs less than 8 years after the first IVF pregnancy, egg freezing was kick-started by an Italian law that restricted the number of eggs that can be fertilized and embryos implanted in IVF procedures as well as forbade the freezing of embryos. Elenora Porcu, M.D., and Raffaela Fabbri, B.Sc., both at the University of Bologna, began experimenting with freezing eggs. Other groups got interested as well, but early rates of live births were dismal.

Slow-rate freezing and vitrification, the two main egg preservation techniques, originated 20 years ago. Methods improved in the mid 90s not only because of more nuanced use of cryoprotectants, but also because of the use of ICSI (intra cytoplasmic sperm injection) to insert sperm directly through the egg's envelope, which loses permeability in freezing.

Currently, most labs slow-freeze eggs immersed in a sodium chloride-containing media, with 1,2 propanediol and sucrose. Some labs use a sodium-depleted media by substituting choline chloride for sodium chloride. In vitrification, eggs are exposed to high concentrations of toxic cryoprotectants for short periods, then abruptly supercooled in liquid nitrogen. Due to their size, eggs have a relatively low surface to volume ratio. Thus, the high cooling rate that is necessary to vitrify water is harder to achieve. Ice crystals can form in the thawing process as well.

## Overcoming the Humpty Dumpty Syndrome

Anywhere from 200 to 400 babies have been born from frozen eggs so far. [1] Sperm and embryos are routinely frozen, producing hundreds of thousands of births in the last few decades, but unfertilized eggs don't like the cold. "A cleaved embryo is not the same volume; it is subdivided" says Thomas "Rusty" Pool, scientific director of the Fertility Center of San Antonio. As an unfertilized egg is a large cell with a high water content, freezing can damage its cytostructure, causing its meiotic spindle, which holds the DNA, to disassemble. If it doesn't properly reassemble in thawing, the chromosomes can get scrambled. Freezing also affects the permeability of the egg's shell. Could freezing lead to birth defects? "We have no way of judging a good egg yet." Pool said. "The long term safety and efficacy are not known."

## ViaCell Branches into Egg Banking and Media

In July, the FDA approved Boston-based ViaCell (http://www.viacellinc.com) to commence a clinical trial evaluating the safety of ViaCyte, a choline chloride-based cryoprotectant media. The product is based on the work of Jacques Cohen, Ph.D., scientific director at the Institute for Reproductive Medicine and Science at St. Barnabas in New Jersey. The trial will enroll 300 healthy women between 21 and 35 years of age in the United States and other countries, whose husbands suffer from male factor infertility.

Participants will get discounted IVF services. The primary efficacy endpoint is 50 live births.

ViaCell, a public 270 employee company, was incorporated in 1994 and is capitalized at $50 million with no debt. According to Marc Beer, president and CEO, ViaCell had $54 million in sales last year from its cord banking business and is conducting research in the areas of cancer, cardiac disease, and diabetes. The company also collaborates with Amgen on cancer therapies.

Getting into the egg freezing business is a strategic move for a company that markets umbilical cord blood banking to anxious parents-to-be, as it relies heavily both on its expertise in cell preservation as well as a marketing network that focuses on consumer education, sending cord blood brochures to hospital waiting rooms and advertising in pregnancy magazines. "The vast majority [of clients] don't have a history of diseases," said Beer. "They are really buying it to be an insurance policy." According to Beer, the company's cord blood business has an 81% gross profit margin.

"If you want to volunteer for this [egg freezing], you are taking a huge risk," said Jacques Cohen. "You only have eggs from one cohort. Even from the best clinic,…you better do this three times. The risk is like any medical procedure. They [ViaCell] are pioneers. They may be 5–10 years too early… From a patient point of view, I'd talk her out of it. I'm biased, because I need this technology to work. Once the trial results are in, I may change my mind."

## Extending Fertility Insurance

Another enterprising company is Boston-based Extend Fertility (http://www.extendfertility.com), started by entrepreneur Christy Jones 3 years ago. The company partners with a network of six fertility centers with 20 locations to offer egg freezing services. Extend uses a slow freezing protocol. About 70% of their 200 clients have frozen their eggs because of delaying childbearing. The remainder are cancer patients or face conditions that could impair their fertility.

According to Charlotte Frank Sage, director of clinical affairs and operations, similar technology resulted in over 70 births at the Porcu lab in Bologna. Extend recommends that its clients freeze about 20 eggs for best results. About a third of their clients have opted for multiple rounds. The company's client cutoff age is 40, but if a younger woman's FSH (follicle stimulating hormone) levels and antral follicle counts, which indicate egg reserve, exceed normal boundaries, they will decline her. Extend's success depends on heavy consumer education, as younger women who would get the best results may not necessarily feel any urgency to freeze their eggs.

Dr. Alan Copperman, Extend's medical director, says he was convinced to join the program by a study of four women using donor eggs, three of whom became pregnant and gave birth. Extend Fertility claims nine births in their satellite centers using their technology in various studies, but, so far, none of their clients have thawed their eggs to attempt pregnancy [2].

Freezing eggs with Extend costs between US $10,000 and $13,000 per cycle, plus the cost of fertility medications, which can range from $2,000 to $5,000—a total of $12,000–$18,000 per cycle. Extend's storage fees are $440 per year.

## Sorting the Numbers

In 2006, Dr. Kutluk Oktay and colleagues at the New York Presbyterian Hospital – Weill Medical College of Cornell University published a meta-analysis of egg freezing data aggregated from various centers. Between 2002 and 2004, for 476 slow-frozen thawed eggs, the fertilization rate was between 60% and 65%, but only about 5% of total frozen eggs resulted in live births. Dr. Oktay then looked at the figure per transfer (only viable embryos were transferred) and calculated a rate close to 38% of clinical pregnancies and 32% of live births; therefore, it took approximately 20 eggs to get one baby. This is half the rate of success of an IVF cycle, which at best averages about 60% chance of pregnancy per cycle. In the last few years, a number of groups around the world are reporting higher rates of fertilization and live births after freezing, but much of that data remains unpublished.

"Our data suggest that the live birth rate is better than 4% per frozen egg, probably more like 5% or 6%," said Richard Paulson, medical director, USC Fertility. "But even if you accept the average of the reported series as being 4% per frozen egg, that still adds up to about 50% aggregate probability of a baby from one batch of frozen eggs (our series had 55%). With these numbers, I don't think that it is reasonable any longer to deny access to this technology to well-informed individuals who wish to preserve their eggs for the purpose of future fertility."

An ongoing randomized trial comparing slow freezing with vitrification is being conducted by Gary Smith, Ph.D., director of the Assisted Reproductive Technologies Laboratory at the University of Michigan, with colleagues in Brazil. As of April, 170 patients (average age 32) engaging in IVF cycles are freezing any eggs over ten retrieved. The endpoint is 40 pregnancies, but there is not enough data yet. "Right now we take 21 oocytes per pregnancy for vitrification and 45 to achieve a pregnancy for slow rate freezing." Smith said.

"You have to look at the denominator," says Dr. Glenn Schattman, associate professor of Obstetrics and Gynecology at the New York Presbyterian Hospital – Weill Medical College of Cornell University. "How many eggs do they need to freeze and thaw, and how many have they transferred back to people? …There is not verifiable auditable data. I think that women need to be told. I think that ASRM's [American Society for Reproductive Medicine] policy, it is the bottom line [that] it is still research. They should not base their childbearing or future family on it."

Fertility insurance is a fine concept, but since there is little published, peer-reviewed data, a woman paying per cycle should know the live birth rate per egg extraction cycle at her chosen clinic. The only guarantee in the world of assisted reproduction is that peace of mind does not come cheaply. The number of eggs necessary to get a baby will also vary due

 

to her age and egg quality. She can bet the bank that success rates will eventually get better, but in the meantime, to improve her odds, she could simply fertilize her extracted eggs with donor sperm and freeze the embryos.

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